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Interleukin-17 and systemic lupus erythematosus: current concepts

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Summary

The emerging role of interleukin (IL)-17 as a hallmark proinflammatory cytokine of the adaptive immune system, produced primarily by a new T helper cell subset termed 'Th17', has received considerable attention. Differentiation of Th17 cells is driven by the simultaneous presence of transforming growth factor-β and certain inflammatory cytokines (e.g. IL-6, IL-21), and recent studies have shown that inflammation instigated by IL-17-producing cells is central to the development and pathogenesis of several human autoimmune diseases and animal models of autoimmunity. In this review, we focus on the information regarding IL-17 and systemic lupus erythematosus (SLE), a chronic autoimmune disease. The work that has explored the development and behaviour of IL-17-producing cells in SLE is discussed, and different mechanisms by which IL-17 could potentially augment inflammation and autoantibody production in the context of SLE are proposed.

Keywords: autoimmunity, DN T cells, IL-17, SLE, Th17

Interleukin-17-producing T cells and autoimmunity

Originally termed cytotoxic T lymphocyte antigen 8, interleukin (IL)-17 is a 17 kDa type I transmembrane protein isolated initially from a rodent CD4 T cell cDNA library [1]. It represents the prototype of a recently identified family of cytokines that comprises six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F) and five receptors (IL-17RA, IL-17RB, IL-17RC, IL-17RD, IL-17RE) [2–4]. The most closely related members of the family are IL-17A and IL-17F, both of which are produced mainly by activated T cells [5] and bind to the same receptors (IL-17RA and IL-17RC) [6]. Thus, the dissection of their individual contributions to normal and abnormal immune responses has been complex and is not understood completely [7,8]. Although the signalling pathway downstream of IL-17R remains to be elucidated, recent studies have shown that nuclear factor-κB and mitogen-activated protein kinase pathways are involved [9,10].

In addition to its potent proinflammatory capacity, IL-17 exerts its effects through the recruitment of monocytes and neutrophils by increasing the local production of chemokines (IL-8, monocyte chemoattractant protein-1, growth-related oncogene protein-α) [11–15], the facilitation of T cell infiltration and activation by stimulating the expression of intercellular adhesion molecule-1 [16] as well as the amplification of the immune response by inducing the production of IL-6, prostaglandin E_2, granulocyte–macrophage colony-stimulating factor and granulocyte colony-stimulating factor [17,18]. Additionally, IL-17 synergizes with other cytokines, in particular with IL-1β, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ [19–22]. IL-17RA is expressed broadly and mediates its effects through a number of immune and non-immune cells (particularly endothelial and epithelial cells) [23].

The IL-17 is produced by several cell types that include $CD4^+$ T cells, $CD8^+$ T cells, $CD3^+CD4^-CD8^-$ T cells, γδ-T cells, natural killer cells and neutrophils [24]. IL-17 plays an important role in the immune response against certain pathogens, particularly bacteria (e.g. *Klebsiella pneumoniae*, *Citrobacter rodentium*, *Borrelia burgdorferi*) [25–27] and fungi (e.g. *Candida albicans*) [28]. In concordance, human and murine antigen-presenting cells (APC) induce the differentiation of naive T cells into IL-17-producing cells when incubated with certain microbial products such as lipopolysaccharide, peptidoglycans and zymosan [29,30].

The $CD4^+$ T cell effector subset termed 'Th17' has been considered a remarkable discovery which was named after its signature cytokine, IL-17 [31]. Th17 cells are considered as a distinct T helper cell subset because: (i) they arise from naive T cells when primed in the presence of specific factors; (ii) their differentiation is controlled by exclusive transcription factors; (iii) they exhibit a particular cytokine production

profile; and (iv) their differentiation into Th17 cells excludes the acquisition of other effector phenotypes (i.e. Th1 and Th2). The concept of Th17 cells was conceived within the setting of experimental autoimmune diseases and these cells have, since their first description, been associated intimately with autoimmune responses.

The IL-23 is a heterodimer consisted of two subunits, p19 and p40 [32]. Although p19 is exclusive to IL-23, p40 is also part of IL-12 (when combined with p35). The discovery of p19, in 2000, implied that p40-deficient mice were not only IL-12-deficient (as considered hitherto) but also IL-12- and IL-23-deficient. The subsequent comparison between IL-23p19-deficient mice and IL-12p35-deficient mice demonstrated that the absence of IL-23 (rather than the absence of IL-12 and thus Th1 cells) protected mice from experimental autoimmune encephalitis (EAE) [33]. IL-23 was necessary for the development of a pathogenic Th17 response that could be transferred into naive wild-type mice upon T cell adoptive transfer [34]. These discoveries, along with the fact that IL-23 increases IL-17 production by memory T cells [23], suggested the presence of a novel T helper functional axis formed by IL-23 (as an IL-17-inducing APC-derived factor) and IL-17 (as the product of the differentiated T cell) analogous to the IL-12/Th1 system. Further work demonstrated that naive T cells lack IL-23R and that this cytokine contributes to the expansion and maintenance of the Th17 subset rather than to its differentiation [31,35].

The combination of IL-6 and transforming growth factor (TGF)-β was shown to induce the differentiation of murine naive T cells into Th17 cells [36–38]. This notion is extremely interesting, as it implies that the presence of an inflammatory signal (i.e. IL-6) is the key element that determines whether naive T cells become proinflammatory (i.e. Th17) or suppressive (regulatory T cells). Accordingly, IL-6-deficient mice are resistant to EAE induction and have defective Th17 cell differentiation [37,39]. The specific contribution of TGF-β, which is apparently able to induce both suppressive and inflammatory cells, as well as the particular instances when it participates in T cell priming, will need to be addressed in future studies. IL-21, a cytokine related to IL-2 [40], is also able to induce T cell differentiation into Th17 cells [41–43]. Contrary to IL-6, IL-21 is not produced by APCs but by T cells – particularly Th17 cells and T follicular helper cells (T_{FH}) – and thus has been postulated to act as an autoamplifier of the Th17 response [41–43]. Differentiation of human naive T cells into Th17 cells is accomplished similarly when TGF-β is present along with IL-21, or different combinations of IL-6, IL-23, IL-1β and TNF-α [44–46].

The genetic programme responsible for driving the Th17 phenotype is accomplished by at least three transcription factors. Two of them belong to the family of retinoid-related orphan receptors (RORγt and RORα). RORγt is expressed selectively in Th17 cells and its presence is necessary for IL-17A and IL-17F production [47]. RORα, however, can also promote Th17 differentiation [48]. Both factors are induced by TGF-β and IL-6 through a signal transducer and activator transcription-3-dependent mechanism [48]. The relative contribution of these transcription factors to Th17 differentiation and behaviour, during normal and abnormal immune responses, is still unknown.

In summary, IL-17 is a potent proinflammatory cytokine produced by activated T cells, particularly Th17 cells. Although necessary in the responses against bacteria and fungi, IL-17 has been associated with the pathogenesis of a wide range of inflammatory and autoimmune diseases including psoriasis, rheumatoid arthritis (RA) [49,50], inflammatory bowel disease [51], systemic sclerosis [52] and systemic lupus erythematosus (SLE) [53,54].

Murine models of IL-17 and SLE

From a conceptual point of view, IL-17 and Th17 cells were regarded initially as potentially involved in diseases considered formerly to be driven by Th1 cells. Thus, early investigations focused upon EAE [34] and murine models of RA [55,56], and it was found that inhibition of IL-17 (or IL-17-producing cells) was beneficial. Th17 cells were eagerly considered part of the pathogenesis of such diseases as powerful effector cells able to amplify organ-specific destructive inflammatory responses by means of producing chemokines and cytokines. Although SLE has been considered classically an autoantibody- and immune complex-driven disease, recent work indicates that IL-17 is involved in different aspects of its pathogenesis. Its potent proinflammatory capacity, along with the effects it exerts in a variety of cells, suggests that its unregulated production has indeed widespread consequences in animals and patients with lupus (Tables 1 and 2). Lupus-prone mice (MRL/*lpr*) are particularly susceptible to the development of inflammation induced by ischaemic insults [57]. We have shown that

Table 1. Interleukin (IL)-17 in murine models of systemic lupus erythematosus.

Murine models	Experimental evidence and outcomes	References
MRL/*lpr*	Enhanced IL-17-mediated tissue injury after ischaemia reperfusion	Edgerton *et al.*, 2009 [58]
BXD2	Increased numbers of IL-17-producing T cells provide help to B cells and stimulate spleen germinal centre formation. IL-17 over-expression enhanced disease; IL-17R blockade reduced its intensity	Hsu *et al.*, 2008 [62]
SNF_1	Increased numbers of $IL\text{-}17^+$ cells	Kang *et al.*, 2007 [59]
Ets-1 knock-out	Enhanced differentiation of naive T cells into Th17 cells	Wang *et al.*, 2005 [68]

Table 2. Interleukin (IL)-17 in human SLE.

Experimental evidence and outcomes	References
Significant levels of IL-17 and IFN-γ detected in double-negative T cells from SLE patients	Crispin *et al.*, 2008 [53]
Elevated levels of IL-23 and IL-17 in sera from SLE patients	Wong *et al.*, 2008 [54]
IL-17 increases autoantibody production from PBMC in patients from lupus nephritis	Dong *et al.*, 2003 [64]

IFN, interferon; SLE, systemic lupus erythematosus; PBMC, peripheral blood mononuclear cells.

intestinal injury following ischaemia and reperfusion is mediated, at least partially, by $CD4^+$ T cells that produce IL-17, and that this phenomenon is augmented in MRL/*lpr* mice [58]. Accordingly, $CD4^+$ T cell depletion suppressed injury induced by ischaemia and deficiency of IL-17 (in IL-23p19$^{-/-}$ mice) reduced tissue injury significantly. The reduction in tissue injury observed in the absence of IL-17 was more pronounced in MRL/*lpr* mice than in non-autoimmune B6 mice [58]. This effect is probably due to the fact that MRL/*lpr* mice have a higher frequency of IL-17-producing T cells (unpublished data, Tsokos Laboratory).

Splenocytes from lupus-prone SNF_1 mice (New Zealand black × SWR F_1) produce significantly higher amounts of IL-17 than splenocytes from non-autoimmune C57Bl/6J (B6) mice when cultured in the presence of nucleosomes [59]. Moreover, IL-17-producing T cells were detected in kidneys affected by nephritis in SNF_1 mice. Importantly, clinical improvement achieved either by tolerance induction with a histone-derived peptide [59] or with nasal administration of anti-CD3 [60] was accompanied by decreased IL-17 production, decreased percentage of IL-17-producing cells and abrogation of IL-17^+ kidney-infiltrating cells [59]. Interestingly, in the first of these reports, tolerance induction was associated with decreased IL-6 production and increased TGF-β production that paralleled a reduction in the fraction of IL-17-producing T cells and a reciprocal increase in regulatory T cells [59]. This highlights the fact that the SLE microenvironment is particularly apt for the differentiation of IL-17-producing cells.

The BXD2 mouse, a lupus model that develops arthritis, glomerulonephritis and autoantibodies spontaneously [61], has high IL-17 levels in serum as well as increased numbers of IL-17^+ cells in the spleen [62]. Accordingly, upon stimulation an increased fraction of BXD2 T cells produce IL-17. The humoral response is augmented strongly in these mice [63]. They develop germinal centres (GC) spontaneously in the spleen, where IL-17^+ T cells co-localize with IL-$17R^+$ B cells [62]. The importance of IL-17 in this process was demonstrated when B6 and pre-disease BXD2 mice were infected with an IL-17-coding adenovirus that increased IL-17 levels and induced the formation of GC in both mouse strains. Concordantly, formation of GC diminished and production of anti-DNA and anti-histone antibodies was abrogated in BXD2 IL-17R-deficient mice [62]. This study indicates that besides acting as a mediator of inflammation, IL-17 can also provide help to B cells, a notion suggested by a former report that showed that IL-17 increased immunoglobulin (Ig)G and anti-DNA antibody production in mononuclear cells derived from SLE patients [64].

Intriguingly, a recent paper describes a T cell effector population akin to T_{FH} [65] that provides help to B cells in an extrafollicular location, a phenomenon observed in several lupus-prone strains (e.g. MRL/*lpr* and NZB × W F_1) [66]. Extrafollicular helper cells provide B cell help via IL-21 and CD40L and their development depends upon the presence of inducible co-stimulatory molecule [66]. Along with IL-21, these cells produce IL-17, but IL-17 does not seem to play an essential role in B cell stimulation [66]. On the other hand, the IL-17-inducing capacity of IL-21 has been proposed to contribute to the autoimmune response, because mice with deficient IL-21 signalling have reduced numbers of Th17 cells [41]. However, in BXSB-*Yaa* mice, IL-21R deficiency abrogated autoimmune disease without affecting IL-17 levels or reducing the frequency of IL-17-producing cells [67]. Thus, although IL-21 derived from follicular helper T cells seems to play a role in B cell stimulation in autoimmune murine models, its contribution to Th17 cell differentiation is still debatable. Similarly, although in certain conditions IL-17 has proved to be able to provide B cell help, the precise contribution of IL-17 derived from T_{FH} cells to GC formation and antibody production will have to be defined more clearly.

The Ets-1 knock-out mouse is another mouse model which demonstrates a potential pathogenic role for IL-17-producing T cells. Ets-$1^{-/-}$ mice display high levels of IgG and IgM autoantibodies, leading further to the deposition of immune complexes in kidney glomeruli and complement activation [68]. Although elevated serum levels were not detected in these Ets-1 knock-out mice, increased levels of IL-17A, IL-17F and IL-22 mRNA were found in the lung, consistent with process of inflammation in this tissue.

A recent report grants TNF-α a protective role in SLE. Jacob *et al.* studied NZM2328 mice deficient in both TNF-α receptors and found that disease severity (in terms of nephritis and production of anti-DNA antibodies) increased when the TNF-α pathway was disrupted. The effect depended upon the presence of $CD4^+$ T cells that exhibited a Th17 gene profile. This suggests that acceleration of nephritis in SLE may indeed be associated with the IL17/Th17 pathway [69].

Mechanisms of autoimmune pathology: IL-17 and human SLE

The SLE is a complex autoimmune disease in which a T cell-driven autoimmune response against ubiquitously

expressed autoantigens results in clinically and pathologically diverse manifestations [70]. Although the presence of a large array of autoantibodies is perhaps the most conspicuous characteristic of SLE patients, target organ infiltration and chronic inflammation are essential pathogenic features that result in end-organ damage in most SLE clinical manifestations (i.e. nephritis, vasculitis, discoid lupus) [71]. Recent evidence indicates that IL-17 plays a role in the pathogenesis of SLE [72]. SLE patients have higher serum levels of IL-17 and IL-23 than healthy controls [54,73]. Moreover, the frequency of IL-17-producing T cells is increased in peripheral blood of SLE patients [53,54]. Accordingly, IL-17 production is increased in *in vitro* stimulated lymphocytes from SLE patients when compared with normal lymphocytes [54]. Plasma IL-17 levels show a positive correlation with SLE disease activity [54].

In a recent work, we demonstrated that a significant fraction of the IL-17 produced in SLE patients derives from double-negative (DN) TCR-$\alpha\beta^{+}CD4^{-}CD8^{-}$ T cells [53]. Scarce in healthy individuals, DN T cells are expanded in peripheral blood of SLE patients and produce IL-17 and IFN-γ. Furthermore, DN T cells and IL-17-producing T cells are found in kidney biopsies from patients with lupus nephritis [53]. Along with IL-13, IFN-γ and IL-17 were the main cytokines produced by infiltrating T cells in nephritic kidneys of MRL/*lpr* mice [74]. The finding of DN T cells within a T cell infiltrate demonstrates their capacity to accumulate in inflamed tissue and suggests strongly that they play a pathogenic role in the local inflammatory response [53]. Similarly, the demonstration of $IL\text{-}17^{+}$ T cells in kidneys affected by lupus nephritis indicates that it may play a role in the amplification and perpetuation of the inflammatory response in organs targeted by SLE.

Apart from the obvious proinflammatory activities attributed to IL-17, its effects in other cell types may contribute to SLE pathogenesis. Accordingly, increased production of total IgG, anti-dsDNA IgG and IL-6 by peripheral blood mononuclear cells of patients with lupus nephritis was observed when they were cultured with IL-17 [64]. These findings suggest that IL-17 may participate in the activation of B cells in patients with SLE (Table 2).

Concluding remarks and perspectives

In this communication, we have reviewed reports that address the relationship between IL-17 and SLE. Virtually, all papers indicate that IL-17 production is increased in patients with SLE as well as in animals with lupus-like diseases. This could be a consequence of systemic inflammation and augmented T cell activation [75], or could indicate that the pathways that guide T cell differentiation into IL-17-producing cells (either Th17 or DN T cells) are facilitated in SLE patients (Fig. 1). This possibility is plausible because IL-6 [76] and IL-21 production (unpublished data, Tsokos Laboratory) has been found increased in patients with SLE. Moreover, the reciprocal regulatory T cell deficiency reported in SLE patients [77] could also be a consequence of skewed T cell differentiation. These issues will have to be addressed specifically in future studies.

Evidence obtained in human samples places IL-17 in the midst of the inflammatory reaction in SLE patients [53]. Although a causal association cannot be sought in human

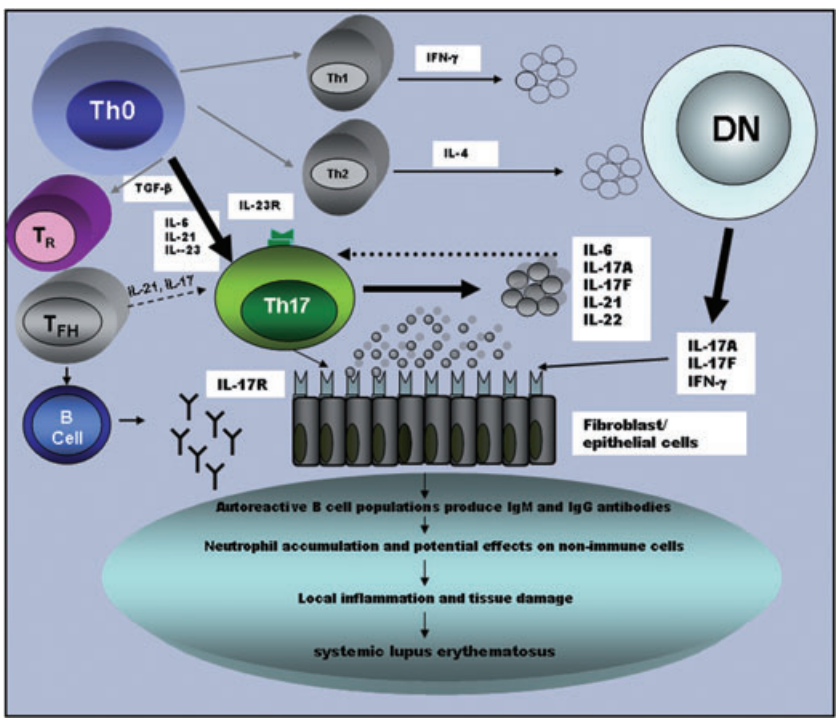

Fig. 1. Proposed model for the role of T helper type 17 (Th17) cells and interleukin (IL)-17 in the pathogenesis of systemic lupus erythematosus (SLE). $CD4^{+}$ T cells differentiate into Th1, Th2 and Th17 effector subsets. The cytokine milieu characteristic of SLE patients (lack of IL-2, high levels of IL-6 and IL-21) could promote Th17 cell expansion. Th17 cells serve as an independent T helper effector cell subset promoting inflammation through cytokine secretion. The hallmark cytokines associated with Th17 cells include IL-17A, IL-17F, IL-21 and IL-22. These cytokines have stimulatory effects on B cells, and instigate local inflammation and tissue damage leading subsequently to the pathogenesis of SLE.

studies, animal models have demonstrated that blockade of IL-17 decreases lupus manifestations [62]. Interestingly, information obtained in these studies suggests that IL-17 could be associated not only with T cell-mediated tissue injury but also with production of pathogenic autoantibodies. SLE-derived B cells have been shown to increase anti-DNA production when cultured in the presence of IL-17 [64]. The relative importance of this pathogenic mechanism in human SLE remains to be demonstrated in future work.

The evidence provided in this review describes IL-17 as an important cytokine in the pathogenesis of SLE. Its exact place within the mechanisms that lead to SLE remains to be defined. IL-17 might represent an effector cytokine associated to tissue damage and disease amplification or perhaps a cytokine whose abnormal presence during otherwise normal immune responses causes tolerance disruption. These issues, as well as the main question of whether IL-17 blockade will be therapeutically useful for SLE patients, will be addressed in the near future [78,79].

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